Gram-Positive Rods

Introduction

All of the organisms in this lesson are Gram-positive rods. The main division of the lesson is between spore-forming rods (*Bacillus* and *Clostridium*) and those Gram-positive rods that do not form spores (diphtheria, *Listeria*, *Nocardia*, and *Actinomyces*). Normal taxonomy would have you use aerobic/anaerobic and motile/nonmotile first, then divide by spores at the end of the decision tree. This isn't helpful to medical microbiology and your learning the bugs, keeping them straight. Every bug in this lesson is a Gram-positive rod, and the only Gram-positive rods you need to know. Then you break it down into spore former vs. non-spore former. Then you learn the diseases they cause, incorporating the details of (an)aerobic and (im)motile into the illness script of the disease. This approach is much more in tune with clinical microbiology.

We do a spore-former overview, then engage the diseases *Bacillus* (the serious anthrax and the not-so-*Cereus* diarrhea) and *Clostridium* (gas gangrene, tetanus, botulism, and *C. diff* colitis) cause. We then change gears and do a non-spore-former overview before engaging the individual bacteria and the diseases they cause in more detail. The spore formers monopolize the discussion because they are so high-yield.

Spore-Forming Gram-Positive Rods

Bacillus and *Clostridium* are both **spore-forming** Gram-positive rods. *Bacillus* is **aerobic** and *Clostridium* is **anaerobic**. The details of microbiology physiology, then, come down to the differences between species, within each genus. For *Bacillus*, *Bacillus anthracis* **has a capsule** and is **immotile**; *Bacillus cereus* has no capsule and is motile. For *Clostridium*, *perfringens* is **immotile**; the rest are motile. Then what becomes relevant to medical microbiology is the disease they cause, the toxins they use, and what treatments are available for each disease.

	BACTERIA	CAPSULE	MOTILITY	TOXINS	DISEASE	SYMPTOMS
Aerobic	*Bacillus anthracis*	**Capsule, peptide**	**Immotile**	Lethal Protective Edema	Cutaneous	Black painLESS pustules and painFUL lymphadenopathy
					Pulmonary	Pneumonia plus . . . sheep, mediastinitis, spores
	Bacillus cereus	No capsule	Motile	Heat stable	Emesis	1–6 hours after ingestion, emesis, like *Staph. aureus*
				Heat labile	Diarrhea (ETEC)	3–8 hours after ingestion, diarrhea, like ETEC, *Vibrio*
ANaerobic	*Clostridium perfringens*	No capsule	**Immotile**	Lecithinase	Gas gangrene	Soil or feces wound, crepitus in skin, air on imaging
	Clostridium tetani		Motile	Tetanospasmin	Tetanus	Lockjaw, spastic paralysis, pain, death
	Clostridium botulinum			Botulinum toxin	Botulism	Floppy baby syndrome
	Clostridium difficile			Toxin A	Enterotoxin	Enterotoxin watery diarrhea
				Toxin B	Cytotoxin	Pseudomembranous colitis, megacolon

Table 13.1: Spore Formers

Bacillus anthracis ("Anthrax")

Physiology/Structure. *Bacillus anthracis* is **aerobic** (requires oxygen), **spore-forming**, and **immotile**. It is a Gram-positive rod.

Virulence. Virulence comes down to the unusual mechanism of toxin, the polypeptide capsule, and the ability to form spores. Unlike most bacteria that secrete an AB toxin, *Bacillus anthracis* produces three protein components that combine to create toxic effects. The protein components are **protective antigen** (PA), **edema factor** (EF), and **lethal factor** (LF). On their own, the individual proteins do nothing. Protective antigen binds to the target cell's membrane, gets cleaved, and leaves behind pore fragments. The fragments assemble and make a pore through which edema factor or lethal factor can pass. **Edema factor** IS **adenylyl cyclase**, which increases cAMP levels, resulting in edema (much like *Bordetella pertussis* did by ADP-ribosylation of G_s, except *Bacillus anthracis* provides the adenylyl cyclase rather than increasing the activity of endogenous adenylyl cyclase). **Lethal factor** is a zinc-dependent metalloproteinase that cleaves MAP kinases, which leads to cell death (we aren't sure how).

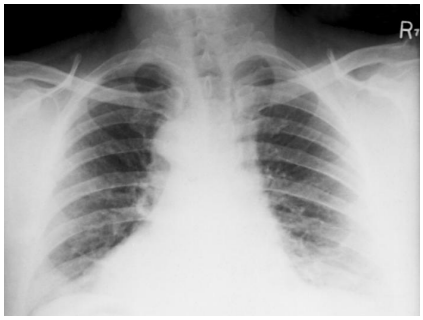
Bacillus anthracis is the **only** bacterium to have a **peptide capsule**. The capsule is made from **poly-D-glutamic acid.** The polypeptide capsule is **antiphagocytic**. The **spores** are inactive, dormant cells, but are highly resistant to drying, desiccation, heat, cold, etc.

Epidemiology. The spores are found **in soil** and **on sheep**. Contact with the spores can cause them to be **inhaled into lungs** or **inoculated into wounds**. Anthrax was formerly a weapon of terrorism. The vast majority of anthrax, the disease caused by *B. anthracis*, is cutaneous and comes in the way of farmers who handle herbivore livestock. The even vaster majority of anthrax is in herbivore livestock; humans act as accidental dead-end hosts. It is the dead-end host diseases we discuss—cutaneous and pulmonary anthrax.

Cutaneous anthrax accounts for 95% of anthrax cases. It begins as a papule, which progresses to include papules with vesicles, and is hallmarked by **black painless pustules** with central necrosis. These pustules are called eschars. They crust over and resolve spontaneously. There is **painful lymphadenopathy** in the region draining the pustules. Rarely does cutaneous anthrax cross to become septic or bacteremia. Because *Bacillus anthracis* is nonmotile, the bacteria grow where they were inoculated (locally) and invade lymph nodes where macrophages bring them. Pustules and regional lymphadenopathy characterize this disease.

Pulmonary anthrax (wool-sorter's disease, bioterrorism) is caused by inhalation of spores. Spores germinate, and the bacteria do to the lung what they did to the skin—grow locally and invade regional lymph nodes. But inhalation distributes the spores throughout the lungs and there is no intact skin protecting alveoli. This widespread infection results in **mediastinal hemorrhagic lymphadenitis** (inflammation of the lymph nodes of the mediastinum that sometimes bleed). It resembles a common pneumonia—fever, cough, cyanosis—but has a diffuse hazy chest X-ray rather than an obvious consolidation. If not treated, it rapidly progresses to shock and death. A rapidly progressive pneumonia and **mediastinal widening on X-ray** with any mention of **sheep** or **mail spores** is anthrax.

Treatment. Treatment is with **ciprofloxacin** or **doxycycline**—penicillin resistance is high. There is a **toxoid vaccine** given to those in high-risk occupations. There is also a vaccine for livestock, so anthrax has predominantly become a disease of impoverished and developing countries.



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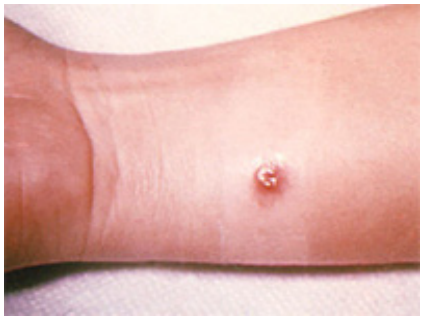

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Figure 13.1: *Bacillus anthracis*
(a) X-ray showing a widened mediastinum in a case of pulmonary anthrax. (b) Cutaneous anthrax showing a black eschar on an arm. (c) An inconspicuous early lesion of a raised sore with a black center.

B. cereus ("Buffet-Line Reheated-Rice Gastroenteritis")

B. cereus has the same look, shape, virulence, and spore formation that *Bacillus anthracis* does, except *B. cereus* **is motile** and **unencapsulated**, the only two features distinguishing it from *Bacillus anthracis*. We said *Bacillus anthracis* for anthrax because the full name gives it more weight in your mind, and the disease it causes is more severe than *B. cereus*. And we seriously want you to say "Bee Serious" whenever you see *B. cereus*. Because, ironically, it isn't very serious at all. Just like the disease it causes. *B. cereus* is the enterotoxin-producing bacterium of **buffet lines** and especially of **reheated rice** at Asian food buffet restaurants (there is nothing special about Asian cuisine, other than that's the scenario in which the exam has presented the disease). *B. cereus* produces two toxins. The heat-**stable** enterotoxin causes **emesis** and is analogous to *Staph. aureus*'s preformed toxin. *Staph. aureus* grows on egg-based and proteinaceous foods, and *B. cereus* on rice, both causing emesis < 6 hours after ingestion. The heat-**labile** *B. cereus* enterotoxin causes a diarrheal illness, induced by an AB toxin that ADP-ribosylates G_S just like ETEC and *Vibrio cholerae*. *B. cereus* contaminates meat and vegetables, and then causes a diarrheal illness > 6 hours after ingestion. The preformed toxin causes emesis; the one that is made after you eat spores causes diarrhea (see Bacteria #3: *Toxins*). The diarrhea and emesis syndrome are short lived and self-limiting.

HOWEVER . . . on practice questions *B. cereus* and reheated rice often present as diarrhea. When you see buffet lines, reheated rice, and gastrointestinal symptoms, choose *B. cereus*. If asked which toxin causes emesis, answer the preformed heat-stable toxin. If asked which toxin causes diarrhea, answer heat-labile. In reality, either toxin can cause both emesis and diarrhea.

Clostridia

Clostridia are **ubiquitous** in soil, water, sewage, and even the GI tracts of animals and some humans. Most clostridia are harmless. The ones we discuss here cause human disease. Clostridia are able to cause disease because of the hardiness of their spores; their ability to survive in harsh environmental conditions; their rapid growth in nutritionally enriched, oxygen-deprived environments; and the numerous toxins they secrete. The toxins take the form of cytolytic toxins, enterotoxins, and neurotoxins. All *Clostridium* species are **anaerobic Gram-positive** and **spore-forming**. All species are **motile** except for C. perfringens, which is immotile.

C. perfringens causes gas gangrene. *C. tetani* causes tetanus, *C. botulinum* causes botulism, and *C. difficile* causes *C. diff* colitis. We talk about each disease, therefore each bacterium, one at a time. Learn them as distinct diseases; silo them apart from one another. Do NOT group them as "clostridia." To reinforce this, we will use only the species names moving forward.

Clostridium perfringens ("Gas Gangrene")

Physiology/Structure. Large, Gram-positive, spore-forming anaerobic rods. They are **immotile** (only *Clostridium* species that is immotile) and **weakly form spores**. While we are keeping it simple by saying that all clostridia form spores, *perfringens* rarely does in vivo or in culture. It is also the only *Clostridium* species that has a **double zone of hemolysis**.

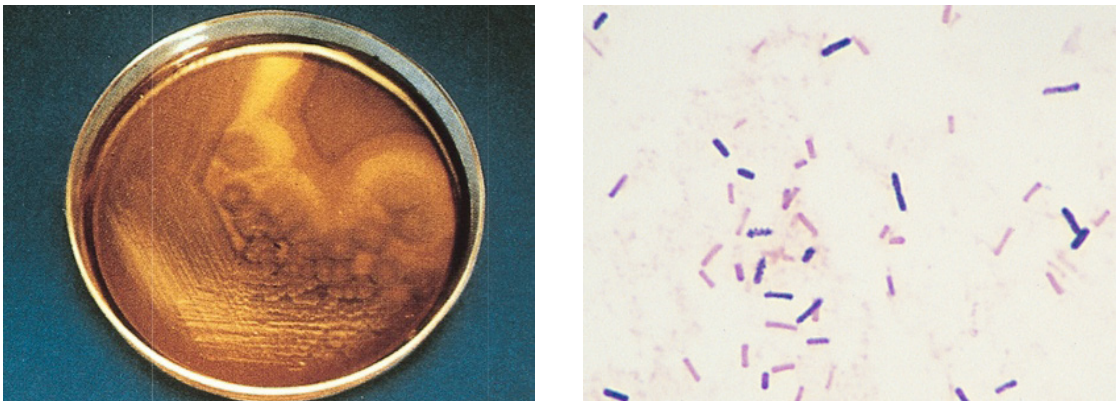


Figure 13.2: *C. perfringens*
A presumptive identification of *C. perfringens* can be made by detection of a zone of complete hemolysis (caused by the θ-toxin) and a wider zone of partial hemolysis (caused by the α-toxin combined with rectangular-shaped Gram-positive rods. Note on the Gram stain the rectangular shape of the rods, the presence of many decolorized rods appearing Gram-negative, and the absence of spores.

Virulence. *Perfringens* produces many toxins. There are two separate diseases caused by two separate toxins you should know of. The **enterotoxin** results in a secretory diarrhea that is always self-limiting. The **α-toxin**, also named **lecithinase,** is a phospholipase and is responsible for destroying the phospholipid membrane of host cells. It is lecithinase that accounts for the rapidly fatal disease gas gangrene.

Epidemiology. While a normal gut flora, spores can hide anywhere. *Perfringens* was the main cause of death from wounds in World War I. Muddy wounds, swamp wounds, and wounds with fecal material are at risk for developing gas gangrene.

Diseases. The **self-limiting watery diarrhea** (not gastroenteritis, only diarrhea) occurs in **reheated meat dishes**. The serious disease is gas gangrene. **Gas gangrene** (termed myonecrosis) occurs in **wounds contaminated with soil or feces**. The spores germinate within the wound, producing **lecithinase** which degrades the membranes of cells—RBCs (hemolysis) WBCs (limited immunity), endothelial cells, and any cells of the tissue it is in (skin, muscle). *C. perfringens* is anaerobic and ferments sugars into **gases like CO_2**, which facilitates the anaerobic environment. It also facilitates diagnosis. If there is **gas in the tissue** (either crepitus felt on exam or gas seen on a radiograph). and especially if the skin is intact, then gas is being made by something inside the patient's limb. The tissue will be tense and tender, and the patient **systemically toxic**. Myonecrosis requires prompt surgical debridement and a **hyperbaric oxygen chamber** for healing, and the use of a translation inhibitor that also covers anaerobes is needed to silence toxin production and kill the anerobic organisms. The only drug that fits that bill is **clindamycin**. Mortality is high, even with treatment.

Toxins are proteins. Proteins are synthesized by ribosomes. The myonecrosis is caused by lecithinase, the α-toxin, not just by bacterial infection. Clindamycin silences ribosomes.

Clostridium tetani ("Tetanus")

Physiology/Structure. Large, Gram-positive, spore-forming, anaerobic rods. *Tetani* is **motile**. Like all clostridia, it is ubiquitous in soil. *Tetani* also loves rust and dirty metal.

Virulence. The spores remain dormant in soil and on rusty dirty metal. When a penetration injury occurs, the bacteria germinate within the **necrotic wound** (which is anaerobic) and produce neurotoxin. The infection itself generally goes unnoticed. In a sense, the virulence is that, other than the wound itself, the patient is unaware that tetanus has gotten in. The incubation period from infection to tetanus syndrome is days to weeks.

Tetanus toxin (tetanospasmin) is an AB toxin. The toxin binds to inhibitory neuron cell membranes, inducing endocytosis. It is carried as a cargo protein up the axon. The toxin then undergoes a conformational change (we're being vague on purpose) within the neuron which allows it to **bind to synaptobrevin,** inhibiting the SNARE complex of vesicles, **effectively eliminating vesicle fusion and exocytosis** of neurotransmitter. Because this effect is found only in motor inhibitory neurons, of vesicles carrying **GABA** and **glycine** (inhibitory neurotransmitters), tetanus toxin **silences inhibitory inputs** to motor neurons. Inhibiting the release of an inhibitor results in disinhibition of motor neurons. This results in the inability to relax muscle contractions, and spontaneous spastic contractions occur. A contraction—voluntary or involuntary—cannot relax.

Disease. Tetanus begins with **trismus** (lockjaw) and **risus sardonicus** (the inability to stop smiling). It progresses to **spastic paralysis—**the inability to move because contractions cannot be relaxed. Without intervention death is the inevitable outcome, resulting from spasm of the diaphragm and suffocation.

Treatment. For someone who already has tetanus syndrome, the goal is to silence the effect of any existing toxin by binding it up with **passive immunity** with **antitoxin IgG**, to make sure no more toxin is made by killing off the bacteria with antibiotics (**metronidazole**), and to prevent suffocation and pain by **reducing spasms** by sedating, paralyzing, and intubating the patient. Paralysis prevents spasms. Paralysis always prevents the diaphragm from breathing, which is what intubating and ventilating the patient is for.

Prevention and Immunity. Passive immunity is conveyed by **immunoglobulin** against the tetanus toxin (antitoxin IgG from the last paragraph). This binds up the toxin and prevents its effects. **Active immunity** is achieved by **vaccination—**after vaccination, the patient will produce their own immunoglobulins against the tetanus toxin. Vaccination is with a **toxoid—**the antigenic portion of the toxin remains, but the toxic portion removed. This is particularly important in tetanus, as the **lethal dose of toxin is less than the antigenic dose of toxin**—infection does not confer immunity. Infection, without intervention, will result in death (see Immunology #13: *Vaccines* for full treatment and prevention algorithms).

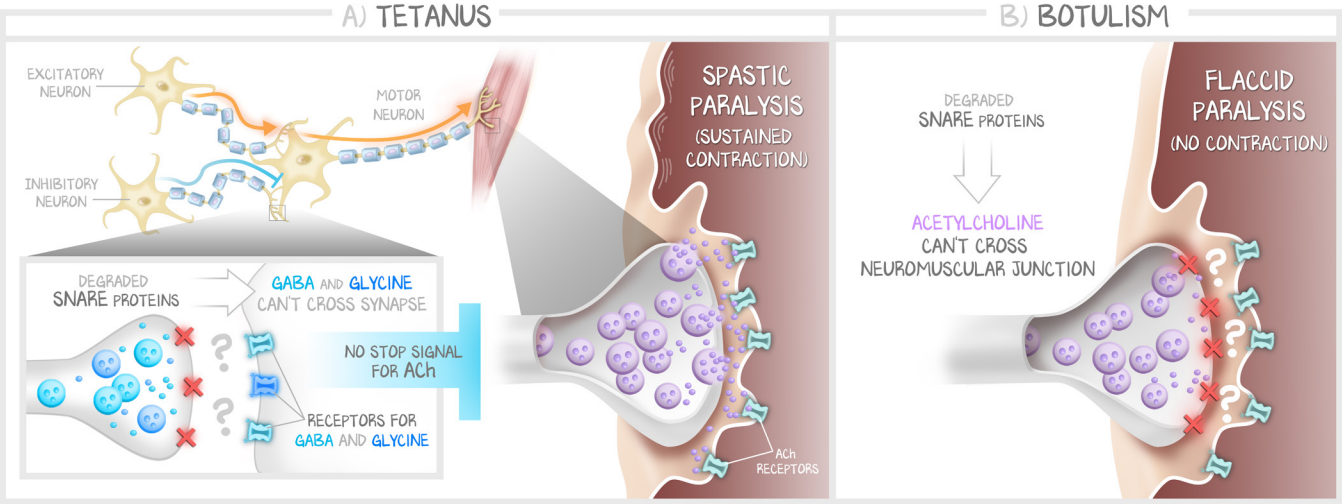


Figure 13.3: Tetanus and Botulism
Yes. You did see this exact image in the Toxins lesson. Here is the content again in the context of the bacteria that cause the symptoms. Both neurotoxins enter a specific neuron and degrade SNARE proteins, preventing the fusion of vesicles carrying neurotransmitters. (a) Tetanus affects exocytosis of vesicles from inhibitory neurons, resulting in disinhibition of the motor pathway and in spastic contractions. (b) Botulism affects exocytosis of excitatory neurons at the NMJ, resulting in the absence of contraction.

Clostridium botulinum ("Botulism")

Physiology/Structure. Large, Gram-positive, spore-forming, anaerobic rods. They are found in the soil, contaminated **self-canned foods**, and in **honey given to infants**. (This is how the test presents them.)

Virulence. *Botulinum* and *tetani* are very similar. The neurotoxin they both secrete is made from a common large protein, cleft in two. Both prevent fusion of exocytosis of neurotransmitter. *Botulinum* toxin has two differences. The first is that it is protected by a complex of non-toxin proteins that allows its survival in the GI tract—eating contaminated food causes disease (tetanus must be inoculated into a wound). The second is that it targets excitatory ACh presynaptic neurons of the neuromuscular junction. With disruption of ACh-vesicle fusion, no excitatory postsynaptic response can be made, and the patient presents with a **flaccid paralysis**.

Adult botulism is caused by **home-canned foods** that are both improperly prepared at the canning stage and improperly cooked when the can is opened. Food contaminated with **pre-formed, heat-labile** toxin is ingested. Proper canning (prevents the infection from starting) or **simply cooking** (not just reheating) **canned foods** can eliminate the toxin. The toxin is absorbed by the gut, and is distributed to all NMJ terminals. Disease begins with **diplopia** and **dysphagia**, progressing to **flaccid paralysis** and eventual death from diaphragmatic respiratory arrest. Treatment is provided simply with **ventilator support**, as the paralysis will wear off. **Antitoxin** can be given to hasten recovery.

Infantile botulism is caused by **ingestion of spore-contaminated honey**. The spores are ingested, germinate, then grow, producing the toxin within the lumen of the gut. Therefore, the symptoms are predominantly gut-related—**constipation**, **feeding problems**—and can progress to **floppy baby syndrome** as the toxin, the same from adult *botulinum*, is absorbed by baby's gut. Death results from diaphragmatic paralysis; treatment is with ventilator support.

Treatment. Antitoxin IgG, ventilator support, antibiotics—just like tetanus, except botulism has no vaccine and does not need paralyzing (because they are already paralyzed). Full recovery may take up to several months. Avoiding contaminated foods and cooking canned foods eliminates the risk of botulism.

"Wound" botulism. Botox®, used to treat wrinkles and hyperhidrosis, is intentionally injected into the area of skin where the effect is desired. Systemic botulism occurs because the spores, and toxins, are ingested. The toxin is absorbed and distributed to all nerve terminals. Locally injected botulism toxin affects only the region where it is injected.

Clostridium difficile ("*C. diff* Colitis")

Physiology/Structure. *C. diff* is a motile *Clostridium* species. It is found in the normal human gut flora. Its resistance to clindamycin, ciprofloxacin, and cephalosporins, and the relative sensitivity of other gut bacteria to these antibiotics, allows it to overgrow the colon. Overgrowth causes illness.

Virulence. *C. diff* produces two toxins. Both toxins are necessary to provoke disease. **Toxin A** is an **enterotoxin** that causes inflammation, weakening of cell junctions, and secretory diarrhea. **Toxin B** is a **cytotoxin** that disrupts protein synthesis and causes disorganization of the cytoskeleton. The other virulence factors shared amongst Clostridium species hold true—anaerobic and spore-forming.

C. diff **colitis** is often a **watery diarrhea** that succeeds **antibiotic use**. It is referred to as pseudomembranous colitis. However, the presence of the **pseudomembrane** (yellow plaque on healthy normal colon) is neither diagnostic (you can have *C. diff* colitis without the pseudomembrane), nor is it sought after (doing a colonoscopy to see the pseudomembrane is dangerous and may lead to perforation). Diagnosis is made with **nucleic acid amplification test (NAAT)** on a sample of diarrhea, finding DNA for the toxin. NAAT for the toxin is superior to *C. diff* antigen detection, though antigen detection was previously widely used until NAAT costs came down. Normally, a culture is the best way to identify bacteria. **Culture is wrong in** *C. diff* colitis because it is normal flora, and a positive culture documents only colonization, not active infection.

Treatment. For **severe disease** (toxic megacolon, renal failure), a combination of **intravenous metronidazole and oral vancomycin** is given. For non-severe disease, **oral vancomycin** is the treatment (formerly metronidazole was the first choice; now no longer). Recurrent infections are treated with **oral vancomycin**. Refractory infections are treated with **fidaxomicin**. Chronic infections that just won't quit are treated with **fecal transplant**. Oral vancomycin is required because IV vancomycin cannot cross the gut barrier and the infection is intraluminal.

Non-Spore-Forming Gram-Positive Rods

This cluster of organisms is sort of the ones left over. Diphtheria and *Listeria* cause their own disease, have their own virulence, and are unrelated to each other and unrelated to the branching bugs. *Actinomyces* and *Nocardia* look like each other on microscopy—branching filamentous rods—but have very little to do with each other in the way of the diseases they cause. *Actinomyces* causes draining sulfur tracts of the mouth and face, and is **anaerobic**, associated with dental surgery and poor dental hygiene. *Nocardia* is **aerobic** and causes pulmonary infections. We discuss each bacterium one at a time.

BACTERIUM	OXYGEN	CAPSULE	MOTILITY	FUN FACTS
Listeria	Aerobic	No capsule	**Motile**	Facultative intracellular, grows at 0°C, deli meat, neonatal sepsis
Diphtheria			**Immotile**	Boring, whooping cough
Nocardia				Branching filamentous rod and acid-fast, pneumonia
Actinomyces	Anaerobic			Branching filamentous rod, NOT acid-fast, sulfur tracts, mouth

Table 13.2: Non-Spore Formers

Listeria monocytogenes ("Pregnant Women, Cheese, and Deli Meats")

Listeria is a small, Gram-positive rod that can **hide within cells** (facultative intracellular parasite) and that exhibits **growth in cold media** even down to 0°C. That means a bacterium is alive, active, and multiplying in refrigerators and even some freezers. It is **motile** via a flagellum, demonstrating explosive movement within eukaryotic cells. *Listeria* also tricks the cytoskeleton into propelling the bacterium through the cell via polymerization of actin filaments (known as comet tails, actin rockets, or actin jets). The actin polymerizes immediately behind the bacterium, pushing it. It appears as though it is moving so fast that it has a trail of actin. It is found as a contaminant of products that are usually refrigerated—**dairy** and **deli meat**.

If a healthy, immunocompetent patient ingests contaminated food, nothing happens at all, or, at worst a mild diarrhea. When *Listeria* encounters **neonates** or **immunocompromised patients**, it can cause **meningitis**. It is the most common cause of meningitis in transplant patients and those on chemotherapy. This is why, in addition to ceftriaxone, vancomycin, and steroids for meningitis, we also add **ampicillin** in the "*elderly neonate taking chemotherapy for the HIV they got from their liver transplant,*" the organizer for "immunosuppression."

Where *Listeria* also gets a lot of play is in the pregnant female. **Pregnant women should avoid deli meat** to reduce risk of exposure. If infected, mom is usually immunocompetent enough to stave off major disease. She is immunocompromised enough (from the parasite growing in her womb) that she may have more than just a diarrhea. Mom does not get meningitis, but may suffer a bout of sepsis, easily treated with β-lactams. But the bacteria get into the bloodstream. And while mom usually survives without sequelae, the fetus does not. In utero transmission of mom's bacteremia to the fetus results in death of the fetus. Should a fetus survive, it will result in **pyogenic granulomas** distributed over the body, resulting in scars, physical retardation, and mental retardation. This condition is called **granulomatosis infantisepticum**. Treating mom does not spare baby. Mom needs to avoid deli meats to avoid *Listeria*.

Corynebacterium diphtheriae ("Diphtheria")

Diphtheria bacteria are small, Gram-positive, aerobic rods that do not form spores. Diphtheria is a disease of the oropharynx. The bacteria **colonize the oropharynx** but do not invade the mucosa. The **diphtheria toxin** is an AB-toxin that **inhibits protein synthesis** via ADP-ribosylation of elongation factor 2 (**EF2**). Infection causes a regular **pharyngitis** at first—fever, malaise, sore throat, and an exudate of the oropharynx. The **grey pseudomembrane** classic to the disease is a product of the **exudate**, **dead mucosal cells**, a fibrin, and lymphocytes. From its location in the oropharynx, the

bacteria secrete the toxin. The toxin is absorbed and distributed through the body via the bloodstream. As the pharyngitis and grey pseudomembrane resolve, the toxin takes effect. The toxin leads to two complications: myocarditis and neurotoxicity. **Myocarditis** (inflammation of the myocardium, which can lead to arrhythmias or heart failure) is found in the majority of diphtheria cases. It also usually resolves spontaneously without further complication, but can be a cause of death. **Neurotoxicity** first affects the nerve local to the disease, but then can progress to peripheral neuritis. Beyond the effects of the toxins, the danger is that the membrane can extend down the oropharynx, leading to **airway obstruction.** Never scrape this lesion, as it will **bleed**, further compromising airway stability. A bleeding mucosal pseudomembrane is unique to diphtheria.

Since vaccination has eradicated diphtheria in the United States, most labs do not store the medium required to culture it. In cystine-tellurite blood agar the tellurite minimizes the growth of non-diphtheria oropharynx organisms, and is reduced by diphtheria, producing the grey-black color on the agar. Degradation of cystine produces a brown halo around the organism. If suspected—**unvaccinated individual returning from endemic areas, with a pseudomembrane—**obtain PCR. The Elek test is now considered obsolete.

Erythromycin and **antitoxin** are used to treat an active infection. Once a cell has bound the toxin, the cell dies. Antitoxin must therefore be administered early in the disease course. Fortunately, the toxin is produced after the tell-tale pseudomembrane is formed, and the toxin's effects are usually after the membrane goes away—there is plenty of time to diagnose and treat. Unfortunately, recognition of the disease requires consideration of a disease with a critically low prevalence—people don't consider it on a differential (because the last case in the US was in 2006). Because diphtheria is ubiquitous in the world, and only eradicated in the United States, this becomes a prime target for board examinations. That way, you will not forget a disease which can readily appear again, one that is easy to treat and fatal if not treated.

This is the "D" of **DTaP vaccination**—the disease can occur only in **immunocompromised** or **unvaccinated** patients.

Branching Filamentous Gram-Positive Rods

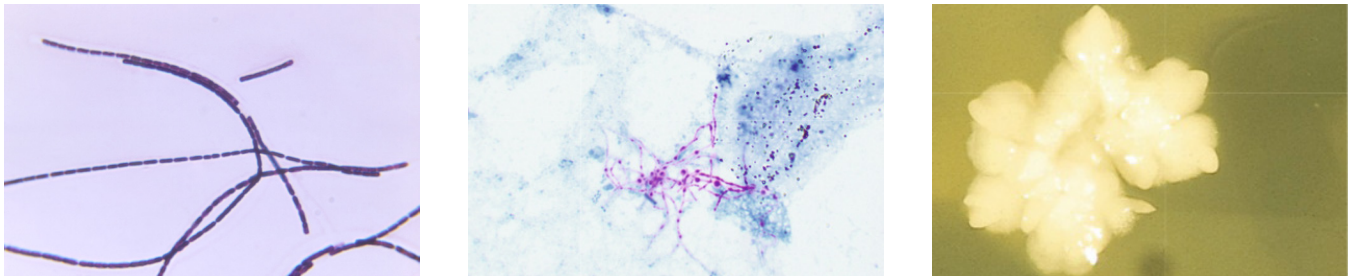
Both *Nocardia* and *Actinomyces* are Gram-positive rods that form long filamentous chains that resemble fungal hyphae. These are both more board favorites than commonly occurring diseases, so we take a test-taking approach with these guys. Learn *Nocardia* and use it to infer *Actinomyces*.

NOCARDIA		ACTINOMYCES
Gram-positive rod Branching filamentous	**Gram Stain**	Gram-positive rod Branching filamentous
Anaerobic	**Growth Conditions**	Aerobic
Acid-fast	**Acid-Fast**	Not
Soil	**Found In**	Oral flora, GI tract
Cavitary lung lesions, cutaneous implantation, can spread to CNS	**Cause**	**Sinus-draining tracts** and forms **yellow sulfur granules**, PID, IUD.
TMP/SMX	**Treatment**	Penicillin

Table 13.3: *Nocardia* vs. *Actinomyces*

Nocardia ("Branching Filamentous Rods 1" and "Cavitary Pneumonia")

Nocardia is one of the two Gram-positive branching rods. *Nocardia* is **aerobic** and weakly stains **acid-fast**. This is helpful in remembering the diseases that *Nocardia* causes, as it mirrors, in a way, the strongly acid-fast organism *Mycobacterium tuberculosis*. *Nocardia* is normally taught in conjunction with mycobacterial organisms. We do not, as it is commonly tested against *Actinomyces*. *Nocardia* causes an indolent **cavitary pneumonia** (like TB), can spread to the CNS (like TB), and can cause **cutaneous** symptoms following traumatic implantation (it's a stretch, but sort of like leprosy, another mycobacterial organism). *Nocardia* is found in the soil, and is inhaled. High-dose sulfonamides (**trimethoprim/sulfa**) can treat *Nocardia* species.



(a) (b) (c)

Figure 13.4: *Nocardia* and *Actinomyces*
(a) The filamentous (stringy) branching rods (thin and long) could be either *Nocardia* or *Actinomyces*. What separates them is that (b) *Nocardia* is weakly acid-fast, and (c) *Actinomyces* is sulfur granules. Of course, not presented is their clinical picture, which also separates them.

Actinomyces ("Branching Filamentous Rods 2" and "Sulfur-Draining Tracts")

Actinomyces is the other branching Gram-positive rod. It is **anaerobic** and does not stain acid-fast. It is a normal part of the vaginal tract, the GI tract, and the mouth. It is known for causing slowly developing infections. These bacteria are highly **invasive**, penetrating all tissue except bone. They are seen in the face and throat and are usually found in people with poor oral hygiene and after surgical procedures in the mouth. *Actinomyces* is thought to be an **endogenous infection** without transmission. *Actinomyces* sets up **abscesses** that are connect by **sinus tracts.** The buzzwords for *Actinomyces* are sinus tracts and **sulfur granules.** They are "sulfur" because they are yellow and smell bad. They are "granules" because they appear macroscopically as firm jagged pebbles. **β-lactams** work well.